

## EFFECTS OF DRUGS IN OPTIMIZING BLOOD PRESSURE AND CARDIAC OUTPUT

SRINIVAS TEJA B\*, KRISHNA SAI V, RAGHU RAM V, RAMA RAO NADENDLA

Department of Pharmacy Practice, Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, Andhra Pradesh, India.

Email: srinivasteja10@gmail.com

Received: 23 September 2014, Revised and Accepted: 23 December 2014

## ABSTRACT

In the cardiovascular system the drug's effects the conditions like peripheral vascular tone, Inotropic state of the heart, chronotropic state of the heart clinically these drugs are used in, acute ischemic heart disease, acute and chronic heart failure, shock (especially cardiogenic), cardiac arrest. When the drugs that are used during the cardiac treatment may give positive results when given in the correct dosage and gives negative results if there is a slight variation in the dose and its frequency.

**Keywords:** Significant effects, Cardiac arrest, Dose adjustment.

## INTRODUCTION

**Amrinone and milrinone**

Amrinone and milrinone are phosphodiesterase III inhibitors that have inotropic and vasodilatory properties. Amrinone has a more significant effect on preload than catecholamines, and the hemodynamic effects are similar to those of dobutamine. Phosphodiesterase inhibitors are approved for use in severe heart failure or cardiogenic shock that is not adequately responsive to standard therapy. Patients who have not responded to catecholamine therapy and patients with tachyarrhythmias are candidates for such treatment. Amrinone may exacerbate myocardial ischemia or worsen ventricular ectopy. Optimal use requires hemodynamic monitoring. The drug is contraindicated with valvular obstructive disease.

Amrinone is administered as a dose of 0.75 mg/kg given initially over 2-3 minutes, followed by an infusion of 5-15 µg/kg per-minute. An additional bolus may be given in 30 minutes.

Like amrinone, milrinone has a relatively long plasma half-life, which makes dose titration more difficult. Milrinone may also be combined with dobutamine at intermediate doses, enhancing the inotropic effects.

A slow intravenous (IV) loading dose (50 µg/kg over 10 minutes) is followed by an IV infusion at a rate of 375-750 ng/kg per-minute for 2-3 days. In renal failure, the dose should be adjusted.

**Calcium**

Although calcium ions play a critical role in myocardial contractile performance and impulse formation, retrospective and prospective studies in the cardiac arrest setting have not shown benefit from the use of calcium. In addition, there is concern on a theoretical basis that the high blood levels induced by calcium administration may be detrimental. When hyperkalemia, hypocalcemia (eg., after multiple blood transfusions), or calcium channel blocker toxicity is present, use of calcium is probably helpful otherwise, calcium should not be used.

When necessary, a 10% solution of calcium chloride can be given in a dose of 2-4 mg/kg and repeated as necessary at 10-minute intervals. (The 10% solution contains 1.36 mEq of calcium per 100 mg of salt per mL). Calcium gluceptate can be given in a dose of 5-7 mL and calcium gluconate in a dose of 5-8 mL.

**Digitalis**

Digitalis preparations have limited use as inotropic agents in ECC. Digitalis decreases the ventricular rate in some patients with atrial

flutter or fibrillation by slowing atrioventricular nodal conduction. The toxic-to-therapeutic ratio is narrow, especially when potassium depletion is present. Digitalis toxicity may cause serious ventricular arrhythmia and precipitate cardiac arrest. Digoxin-specific antibody is available for the treatment of serious toxicity (Digibind, Digitalis Antidote BM).

Digoxin provides safe and effective control of ventricular response rate in patients with chronic atrial fibrillation. Digoxin is less effective in patients with paroxysmal atrial fibrillation and, in general, does not provide adequate rate control in high adrenergic states (such as congestive heart failure, hyperthyroidism, or during exercise). IV calcium channel blockers (diltiazem) or β-adrenergic blockers are now preferred for initial ventricular rate control of atrial fibrillation. In heightened adrenergic states, β-blockers may offer an advantage over calcium channel blockade.

**Dobutamine**

Dobutamine hydrochloride is a synthetic catecholamine and potent inotropic agent useful in the treatment of severe systolic heart failure. Dobutamine has predominant β-adrenergic receptor-stimulating effects that increase myocardial contractility in a dose-dependent manner, accompanied by a decrease in left ventricular filling pressures. An increase in stroke volume frequently induces reflex peripheral vasodilation (baroreceptor mediated) and hence that arterial pressure may remain unchanged. Hemodynamic end points rather than a specific dose should be employed to optimize the use of dobutamine. Hemodynamic monitoring should target the achievement of a normal cardiac output for optimal organ perfusion.

The usual dosage range is 5-20 µg/kg per-minute. However, the individual inotropic and chronotropic responses can vary widely in critically ill patients. Elderly patients have a significantly decreased response to dobutamine. At doses >20 µg/kg per-minute, increases in heart rate of >10% may induce or exacerbate myocardial ischemia. Doses of dobutamine as high as 40 µg/kg per-minute have been used but may be toxic.

**Dopamine**

Dopamine hydrochloride is a catecholamine-like agent and a chemical precursor of norepinephrine that has both α-receptor- and β-receptor-stimulating actions. In addition, there are receptors specific for this compound (DA<sub>1</sub>, DA<sub>2</sub>, dopaminergic receptors). Physiologically dopamine stimulates the heart through both α- and β-receptors. In the periphery, dopamine releases norepinephrine from stores in

nerve endings, but the vasoconstricting effects of norepinephrine are countered by activity at the DA<sub>2</sub> receptors, producing vasodilation in physiological concentration [1]. In the central nervous system, dopamine is an important neurotransmitter. Pharmacologically dopamine is both a potent adrenergic receptor agonist and a strong peripheral dopamine receptor agonist. These effects are dose-dependent.

During resuscitation, treatment with dopamine is usually reserved for hypotension that occurs with symptomatic bradycardia or after return of spontaneous circulation (ROSC). Dopamine in combination with other agents, including dobutamine, remains an option in the management of postresuscitation shock. If hypotension persists after filling pressure is optimized, inotropic (eg., dobutamine) or vasopressor (eg., norepinephrine) therapy is indicated. These therapies correct and maintain systemic perfusion and oxygen delivery.

Dopamine should not be mixed with sodium bicarbonate or other alkaline solutions in the IV line because some data indicates that it may be inactivated in alkaline solutions. Therapy should not be discontinued abruptly but tapered gradually.

The recommended dosage ranges from 5 to 20 µg/kg per-minute. Doses in excess of 10 µg/kg per-minute are associated with systemic and splanchnic vasoconstriction. Higher doses of dopamine, used as a single inotrope/vasoconstrictor, are associated with adverse effects on splanchnic perfusion in some patients.

In the dose range of 2-4 µg/kg per-minute, dopamine is primarily a dopaminergic agonist with little inotropic effect and renosplanchnic perfusion augmentation. In doses of between 5 and 10 µg/kg per-minute, β<sub>1</sub> and β<sub>2</sub> inotropy predominates. In addition, serotonin- and dopaminergic-mediated venoconstriction is noted in this dose range. In doses of 10-20 µg/kg per-minute, α-receptor effects are noted with substantial systemic and splanchnic arteriolar vasoconstriction. Dobutamine, in contrast, is a predominantly β<sub>1</sub>-selective ventricular inotrope that elicits decreased sympathetic nervous tone while augmenting cardiac output.

Dopamine in a dose of 2-4 µg/kg per-minute has been advocated for acute oliguric renal failure. Although dopamine may occasionally promote diuresis, the increase in urine output does not reflect an improvement in renal glomerular filtration rate [2]. Consequently, low-dose dopamine (2-4 µg/kg per-minute) is no longer recommended for the management of acute oliguric renal failure.

Dopamine is available in 5-mL ampules containing 400 mg of dopamine hydrochloride, which when mixed in 250 mL of D<sub>5</sub>W produces a concentration of 1600 µg/mL.

### Diuretics

Furosemide is a potent diuretic agent that inhibits the reabsorption of sodium in the proximal and distal renal tubule and the loop of Henle. Furosemide also has a direct venodilating effect in patients with acute pulmonary edema, but it may have a transient vasoconstrictor effect when heart failure is chronic. The onset of vascular effects is within 5 minutes; however, diuresis occurs later. Furosemide may be useful in the treatment of acute pulmonary edema.

Newer "loop" diuretics that act similarly to furosemide and have a similar profile of side effects include torsemide (1:2 relative potency to furosemide) and bumetanide (1:40 relative potency to furosemide). On occasion, in patients who do not respond to high doses of loop diuretics alone, a combination of such agents with "proximal tubule" thiazide diuretics (such as chlorthalidate or metolazone) may be given. Such combinations require close serial observation of serum electrolytes because profound potassium depletion can result from their use.

The initial dose of furosemide is 0.5-1.0 mg/kg IV injected slowly.

### Epinephrine

Epinephrine hydrochloride produces beneficial effects in patients during cardiac arrest, primarily because of its α-adrenergic receptor-stimulating properties [3]. The adrenergic effects of epinephrine increase myocardial and cerebral blood flow during cardiopulmonary resuscitation (CPR) [4]. The value and safety of the β-adrenergic effects of epinephrine are controversial because they may increase myocardial work and reduce subendocardial perfusion [5].

Although epinephrine has been used universally in resuscitation, there is a paucity of evidence to show that it improves outcome in humans. For a number of years, researchers and clinicians have also questioned the optimal dose of epinephrine. The "standard" dose of epinephrine (1.0 mg) is not based on body weight. Historically a standard dose of 1 mg epinephrine was used in surgical operating rooms for intra-cardiac injections [6]. Surgeons observed that 1-3 mg of intra-cardiac epinephrine was effective in restarting the arrested heart [7,8]. When these and other experts first produced resuscitation guidelines in the 1970s, they assumed that 1 mg of IV epinephrine would work in a similar manner as 1 mg of intra-cardiac epinephrine. Adult patients vary greatly in weight, yet clinicians continue to inject the same 1-mg dose of epinephrine for all body weights.

The dose-response curve of epinephrine was investigated in a series of animal experiments during the 1980s. This work showed that epinephrine produced its optimal response in the range of 0.045-0.20 mg/kg [9,10]. From these studies, it seemed that higher doses of epinephrine were necessary to improve hemodynamics and achieve successful resuscitation, particularly as the interval from cardiac arrest increased. This work led many clinicians to use higher doses of epinephrine in humans, and optimistic case series and retrospective studies were published in the late 1980s and early 1990s [11].

Results from 4 clinical trials then compared high-dose epinephrine with standard-dose epinephrine [12]. Overall the rate of ROSC was increased with higher doses of epinephrine (0.07-0.20 mg/kg); however, no statistically significant improvement in the rate of survival to hospital discharge occurred. On the positive side, these trials failed to detect any significant harm from administration of higher doses of epinephrine. On the basis of this information, in 1992 the guidelines recommended that the first epinephrine dose continue to be 1 mg IV. The 1992 guidelines also recommended that the interval between subsequent doses of epinephrine be every 3-5 minutes rather than every 5 minutes. If the 1 mg epinephrine every 3-5 minutes seemed to be ineffective, the 1992 guidelines accepted the use of higher doses of epinephrine in either escalating doses (1, 3, 5 mg), intermediate doses (5 mg per dose rather than 1 mg), or high doses based on body weight (0.1 mg/kg).

Initial or escalating high-dose epinephrine has occasionally improved initial ROSC and early survival. But 8 randomized clinical studies involving more than 9000 cardiac arrest patients have found no improvement in survival to hospital discharge or neurological outcome, even in subgroups with initial high-dose epinephrine, compared with standard doses [13-18].

These trials largely addressed initial use of high-dose epinephrine and not escalating doses after an initial failure of a 1 mg dose. In these studies, there was no evidence of a worse outcome with high-dose epinephrine. Retrospective studies, however, have suggested that the high cumulative epinephrine dosage is associated with worse hemodynamic and neurological outcome, but they do not prove a causal effect [19,20]. Careful laboratory studies corroborate both beneficial and harmful physiological effects and outcomes. High-dose epinephrine may improve coronary perfusion and increase vascular resistance to promote initial ROSC during CPR, but these same effects may lead to increased myocardial dysfunction and occasionally a severe toxic hyperadrenergic state in the postresuscitation period [21-23]. Target populations with increased risk and potential increased benefit (catecholamine-refractory conditions) need to be identified.

In summary, initial high- IV -dose epinephrine in cardiac arrest may increase coronary perfusion pressure and improve ROSC, but it may exacerbate post-resuscitation myocardial dysfunction. Higher doses of epinephrine have not improved long-term survival and neurological outcome when used as initial therapy. Nor have higher doses definitively been shown to cause harm. Therefore, high-dose epinephrine is not recommended for routine use but can be considered if 1 mg doses fail (Class Indeterminate. Interpretation: Acceptable but not recommended). There is conflicting evidence for and against the use of higher doses of epinephrine (up to 0.2 mg/kg) in cardiac arrest when 1 mg doses have failed (Class IIb: Acceptable but not recommended; weak supporting evidence).

Epinephrine has good bioavailability following tracheal delivery if administered appropriately [24]. Although the optimal dose of epinephrine for tracheal delivery is unknown, a dose that is at least 2-2.5 times the peripheral IV dose may be needed, intra-cardiac administration should be used only during open cardiac massage or when other routes of administration are unavailable [25]. Intra-cardiac injections increase the risk of coronary artery laceration, cardiac tamponade, and pneumothorax. Intra-cardiac injections also cause interruption of external chest compression and ventilation.

The recommended dose of epinephrine hydrochloride is 1.0 mg (10 mL of a 1:10000 solution) administered IV every 3-5 minutes during resuscitation [26]. Each dose given by peripheral injection should be followed by a 20-mL flush of IV fluid to ensure delivery of the drug into the central compartment.

Epinephrine can also be used as a vasopressor agent for patients who are not in cardiac arrest but who have other indications for a vasopressor. For example, epinephrine is considered Class IIb for symptomatic bradycardia (Class IIb: Acceptable but not recommended) after atropine and transcutaneous pacing fail.

#### **Not in cardiac arrest**

Epinephrine hydrochloride, 1 mg (1 mL of a 1:1000 solution), is added to 500 mL of normal saline or D<sub>5</sub>W and administered by continuous infusion. The initial dose for adults is 1 µg/minute titrated to the desired hemodynamic response (2-10 µg/minutes).

#### **Incardiac arrest**

During cardiac arrest, epinephrine may be administered by continuous infusion. The dose should be comparable to the standard IV dose of epinephrine (1 mg every 3-5 minutes). This is accomplished by adding 1 mg of epinephrine hydrochloride to 250 mL of normal saline or D<sub>5</sub>W to run at 1 µg/minute and increased to 3-4 µg/minutes. Continuous infusions of epinephrine should be administered by central venous access to reduce the risk of extravasation and to ensure good bioavailability.

#### **Norepinephrine**

Norepinephrine is a naturally occurring potent vasoconstrictor and inotropic agent. Cardiac output may increase or decrease in response to norepinephrine, depending on vascular resistance, the functional state of the left ventricle, and reflex responses, e.g., those mediated by carotid baroreceptors. Norepinephrine usually induces renal and mesenteric vasoconstriction. It is indicated in patients with severe hypotension (systolic blood pressure <70 mm Hg) and a low total peripheral resistance. Norepinephrine is relatively contraindicated in patients with hypovolemia. Myocardial oxygen requirements may be increased, mandating cautious use of this agent in patients with ischemic heart disease. Ischemic necrosis and sloughing of superficial tissues may result from extravasation of norepinephrine.

Norepinephrine is administered by adding 4 mg of norepinephrine or 8 mg of norepinephrine bitartrate (2 mg of norepinephrine bitartrate is equivalent to 1 mg of norepinephrine) to 250 mL of D<sub>5</sub>W with or without saline, resulting in a concentration of 16 µg/mL of

norepinephrine or 32 µg/mL of norepinephrine bitartrate. The initial dose of norepinephrine is 0.5-1.0 µg/minutes titrated to effect. Patients with refractory shock may require 8-30 µg/minutes of norepinephrine. It should not be administered in the same IV line as alkaline solutions, which may inactivate it.

If extravasation occurs, 5-10 mg of phentolamine in 10-15 mL of saline solution should be infiltrated as soon as possible to prevent necrosis and sloughing.

#### **Nitroglycerin**

Nitrates have been used for their ability to relax vascular smooth muscle. Nitroglycerin is the initial treatment of choice for suspected ischemic-type pain or discomfort. Sublingually administered nitroglycerin is readily absorbed and highly effective in relieving angina, typically within 1-2 minutes. The therapeutic effect may last up to 30 minutes. Nitroglycerin spray may also be used. If the discomfort is not relieved with 3 tablets, the patient should seek emergency medical attention promptly by dialing the appropriate emergency number.

IV nitroglycerin permits more controlled titration in patients with acute coronary syndromes, hypertensive urgencies, or congestive heart failure. IV nitroglycerin is an effective adjunct in the treatment of recurrent ischemia, hypertensive emergencies, or congestive heart failure associated with myocardial infarction (MI). Nitrates should be used cautiously in patients with inferior MI. Nitrates are contraindicated in patients who are preload-dependent with right ventricular infarction. The pharmacological effects of nitroglycerin are dependent primarily on intravascular volume status and to a lesser extent on the dose administered. Hypovolemia blunts the beneficial hemodynamic effects of nitroglycerin and increases the risk of hypotension. Hypotension may reduce coronary blood flow and exacerbate myocardial ischemia. Nitrate-induced hypotension responds to fluid replacement therapy. Other potential complications of IV nitroglycerin include tachycardia, paradoxical bradycardia, hypoxemia caused by increased pulmonary ventilation-perfusion mismatch, and headache. Nitroglycerin should be avoided with bradycardia and extreme tachycardia.

For suspected angina pectoris, 1 nitroglycerin tablet (0.3 or 0.4 mg) is administered sublingually and repeated at 3-5 minute intervals if discomfort is not relieved.

Nitroglycerin is administered by continuous infusion (nitroglycerin 50 or 100 mg in 250 mL of D<sub>5</sub>W or 0.9% sodium chloride) at 10-20 µg/minutes and increased by 5-10 µg/minutes every 5-10 minutes until the desired hemodynamic or clinical response occurs.

Low doses (30-40 µg/minutes) predominantly produce venodilatation; high doses (150-500 µg/minutes) lead to arteriolar dilatation as well. Prolonged administration of nitroglycerin (>24 hrs) may produce tolerance.

#### **Sodium nitroprusside**

Sodium nitroprusside is a potent, rapid-acting direct peripheral vasodilator useful in the treatment of severe heart failure and hypertensive emergencies [27]. Direct venodilatation causes decreases in right and left ventricular filling (preload), resulting in relief of pulmonary congestion and reduced left ventricular volume and pressure. Arteriolar relaxation causes decreases in peripheral arterial resistance (afterload), resulting in enhanced systolic emptying with reduced left ventricular volume and wall stress and reduced myocardial oxygen consumption.

If intravascular volume is normal or high, reduction in peripheral vascular resistance is usually accompanied by an increased stroke volume, minimizing the fall in systemic blood pressure. In the presence of hypovolemia, nitroprusside is likely to cause an excessive drop in blood pressure with reflex tachycardia. Hemodynamic monitoring

is useful when nitroprusside is used. Left ventricular filling pressure should be optimized and maintained at 15-18 mm Hg.

Studies have reported improvement in clinical status in patients with low-output states and high systemic vascular resistance refractory to dopamine, although mortality was not reduced [28]. Nitroprusside has been reported as particularly useful in severe heart failure caused by the regurgitant valvular lesions of aortic insufficiency and mitral regurgitation [29]. Nitroprusside can decrease wall stress and myocardial work in patients with hypertension and acute ischemic heart disease. There is conflicting data about the effects of nitroprusside in patients with acute MI. Some studies indicate an adverse effect in patients treated early after onset [30], contrasting with benefit in others during the same period [31]. Nitroglycerin is less likely to lower coronary perfusion pressure (produce coronary steal) and is more likely to increase blood supply to ischemic areas of the myocardium compared with nitroprusside [32]. Before the reperfusion era, nitroglycerin reduced mortality in acute MI more than the nitroprusside (45% vs. 23%, the relative reduction) [33]. Nitroglycerin is the preferred vasodilator in acute MI, especially when infarction is complicated by congestive heart failure. Nitroprusside may be added when elevated blood pressures are present during acute MI and acute congestive heart failure if nitroglycerin fails to produce optimal levels. Nitroprusside has effects on the pulmonary arterial system. These effects may reverse hypoxic pulmonary vasoconstriction in patients with pulmonary disease (e.g. pneumonia, adult respiratory distress syndrome). This may exacerbate intrapulmonary shunting, resulting in hypoxemia.

The major complication of nitroprusside is hypotension. Patients may also complain of headaches, nausea, vomiting, and abdominal cramps. Nitroprusside is rapidly metabolized to both cyanide and thiocyanate. Cyanide either is metabolized to thiocyanate in the liver or forms a complex with vitamin B<sub>6</sub>. Thiocyanate undergoes renal elimination. Patients with hepatic or renal insufficiency and patients requiring >3 µg/kg per-minute for more than 72 hrs may accumulate cyanide or thiocyanate and should be monitored for signs of cyanide or thiocyanate toxic effects. Cyanide toxicity is detected by the development of metabolic acidosis. When levels exceed 12 mg/dL, thiocyanate toxicity is manifest as confusion, hyperreflexia, and convulsions. Treatment of elevated cyanide or thiocyanate levels includes immediate discontinuation of the infusion. If cyanide levels are extremely elevated and the patient is experiencing signs and symptoms of toxic effects, sodium nitrite and sodium thiosulfate should be administered.

Sodium nitroprusside is prepared by adding 50 or 100 mg-250 mL of D<sub>5</sub>W or saline. The solution and tubing should be wrapped in opaque material because nitroprusside deteriorates when exposed to light. Nitroprusside should be administered with an IV infusion pump.

The recommended dosing range for sodium nitroprusside is 0.1-5 µg/kg per-minute, but higher doses (up to 10 µg/kg per-minute) may be needed.

#### Sodium bicarbonate

Adequate alveolar ventilation is central for control of acid-base balance during cardiac arrest and the postarrest period. Hyperventilation corrects respiratory acidosis by removing carbon dioxide, which is freely diffusible across cellular and organ membranes (e.g., the brain). Little data indicates that therapy with buffers improves outcome. On the contrary, there is laboratory and clinical data indicating that bicarbonate (1) does not improve the ability to defibrillate or improve survival rates in animals; (2) can compromise coronary perfusion pressure; (3) may cause adverse effects due to extracellular alkalosis, including shifting the oxyhemoglobin saturation curve or inhibiting the release of oxygen; (4) may induce hyperosmolarity and hypernatremia; (5) produces carbon dioxide, which is freely diffusible into myocardial and cerebral cells and may paradoxically contribute to intracellular

acidosis; (6) exacerbates central venous acidosis; and (7) may inactivate simultaneously administered catecholamines.

Tissue acidosis and resulting acidemia during cardiac arrest and resuscitation are dynamic processes resulting from low blood flow. These processes depend on the duration of cardiac arrest and the level of blood flow during CPR. Current understanding of acid-base pathophysiology during cardiac arrest and resuscitation indicates that carbon dioxide generated in tissues is poorly perfused during low-blood-flow conditions. Adequate alveolar ventilation and restoration of tissue perfusion, first with chest compressions, then with rapid restoration of spontaneous circulation, are the mainstays of control of acid-base balance during cardiac arrest. Laboratory and clinical data fail to show conclusively that low blood pH adversely affects ability to defibrillate, ability to restore spontaneous circulation or short-term survival. Adrenergic responsiveness also appears to be unaffected by tissue acidosis.

In certain circumstances, such as patients with preexisting metabolic acidosis, hyperkalemia, or tricyclic or phenobarbitone overdose, bicarbonate can be beneficial. After protracted arrest or long resuscitative efforts, bicarbonate possibly benefits the patient. However, bicarbonate therapy should be considered only after the confirmed interventions, such as defibrillation. When bicarbonate is used, 1 mEq/kg should be given as the initial dose. Whenever possible, bicarbonate therapy should be guided by the bicarbonate concentration or calculated base deficit obtained from blood gas analysis or laboratory measurement. To minimize the risk of iatrogenically induced alkalosis, complete correction of the base deficit should be avoided.

#### Vasopressin

Vasopressin is the naturally occurring antidiuretic hormone. In unnaturally high doses much higher than those needed for antidiuretic hormone effects vasopressin acts as a non-adrenergic peripheral vasoconstrictor. Vasopressin acts by direct stimulation of smooth muscle V<sub>1</sub> receptors. This smooth muscle constriction produces a variety of effects, including pallor of the skin, nausea, intestinal cramps, desire to defecate, bronchial constriction, and in women, uterine contractions. Vasopressin, given intra-arterially, is an approved treatment for bleeding esophageal varices because it causes vasoconstriction. Vasopressin also dispels bowel gas shadows during abdominal angiography by causing gastrointestinal smooth muscle constriction. It is usually not recommended for conscious patients with coronary artery disease because the increased peripheral vascular resistance may provoke angina pectoris. The half-life of vasopressin in animal models with an intact circulation is 10-20 minutes, which is longer than that of epinephrine during CPR.

Endogenous vasopressin levels in patients undergoing CPR are significantly higher in patients who survive than in patients who do not have ROSC [34,35]. This finding suggested that exogenous vasopressin might be beneficial during cardiac arrest. After a short duration of ventricular fibrillation, vasopressin during CPR increased coronary perfusion pressure [36], vital organ blood flow, ventricular fibrillation median frequency [37], and cerebral oxygen delivery [38]. Similar results were found with prolonged cardiac arrest and pulseless electrical activity. Vasopressin did not result in bradycardia after ROSC [39].

Interaction of vasopressin with V<sub>1</sub> receptors during CPR causes intense peripheral vasoconstriction of skin, skeletal muscle, intestine, and fat with relatively less constriction of coronary and renal vascular beds and vasodilatation of the cerebral vasculature [40,41]. Vasopressin produces no skeletal muscle vasodilatation or increased myocardial oxygen consumption during CPR because it has no β-adrenergic activity. A combination of vasopressin and epinephrine versus vasopressin alone resulted only in comparable left ventricular myocardial blood flow but significantly decreased cerebral perfusion [42]. Although vasopressin during CPR decreased catecholamine plasma levels in swine [43]

and humans [44] it remains to be determined whether it decreases myocardial oxygen consumption as well. Laboratory studies indicate that the same vasopressin dosage may be administered IV [45,46] and intra-osseously [47].

Repeated doses of vasopressin were more effective than epinephrine in maintaining coronary perfusion pressure above the critical threshold that correlates with successful ROSC [45]. In the post-resuscitation period, vasopressin produces no increased myocardial oxygen demand because baroreceptor-mediated bradycardia in response to transient hypertension remains intact. A reduction in cardiac index in the post-resuscitation phase is transient and fully reversible without administration of more drugs [38]. Although splanchnic blood flow is decreased after successful resuscitation with vasopressin, infusion of low-dose dopamine after CPR can return blood flow to baseline within 60 minutes [48].

Clinically there is preliminary evidence that vasopressin may be effective in enhancing the probability of ROSC in humans with out-of-hospital ventricular fibrillation. In patients with cardiac arrest refractory to standard ACLS, vasopressin induced an increase in blood pressure, and in some cases, ROSC [44]. In a similar clinical evaluation after approximately 40 minutes of unsuccessful ACLS, 4 of 10 patients responded to vasopressin and had a mean increase in coronary perfusion pressure of 28 mm Hg [49]. In a small (n=40) investigation of patients with out-of-hospital ventricular fibrillation, a significantly larger proportion of patients initially treated with vasopressin (40 U IV) were successfully resuscitated and survived 24 hrs compared with patients treated with epinephrine (1 mg IV). There was, however, no difference in survival to hospital discharge [50]. The unpublished manuscript of a larger (n=200), in-hospital clinical trial was reviewed at the time of the Guidelines 2000 Conference. Survival for 1 hr and to hospital discharge was not different whether initial pharmacological treatment was vasopressin or epinephrine (Ian Stiell, MD, oral communication). In this study, response times were short, indicating that CPR outcome achieved with both vasopressin and epinephrine in short-term cardiac arrest may be comparable. Animal and clinical studies as well as *in vitro* studies suggest that vasopressin may be especially useful when the duration of cardiac arrest is prolonged, because the adrenergic pressor response in severe acidosis is blunted. Vasopressin response in severe acidosis remains intact. A large randomized controlled trial evaluating vasopressin versus epinephrine in out-of-hospital cardiac patients is in progress in Europe.

In summary, vasopressin is an effective vasopressor and can be used as an alternative to epinephrine for the treatment of adult shock-refractory VF (Class IIb: Acceptable; fair supporting evidence). Vasopressin may be effective in patients with asystole or pulseless electrical activity as well. Vasopressin should be effective in patients who remain in cardiac arrest after treatment with epinephrine, but there is inadequate data to evaluate the efficacy and safety of vasopressin in these patients (Class Indeterminate).

Vasopressin may be useful for hemodynamic support in vasodilatory shock, such as septic shock and sepsis syndrome. Standard therapy of vasodilatory septic shock includes antibiotics, extracellular volume expansion, vasopressors, and drugs that increase myocardial contractility. Inotropic agents and vasoconstrictor drugs commonly used in this setting may have a diminished vasopressor action [51]. If standard therapy is inadequate, a continuous infusion of vasopressin may be beneficial.

## CONCLUSION

Doses in excess are associated with systemic and splanchnic vasoconstriction. In some case if the standard therapy is inadequate a continuous infusion of the drug by monitoring carefully will give a better therapeutic effect. Proper and the adequate data are necessary to evaluate the safety and efficacy of drugs for cardiac usage.

## ACKNOWLEDGMENT

The author was highly thankful to DR. Gowri (cardiologist) for helping in completing this article.

## REFERENCES

- Farmer JB. Indirect sympathomimetic actions of dopamine. *J Pharm Pharmacol* 1966;18(4):261-2.
- Marik PE. Low-dose dopamine in critically ill oliguric patients: The influence of the renin-angiotensin system. *Heart Lung* 1993;22(2):171-5.
- Yakaitis RW, Otto CW, Blitt CD. Relative importance of alpha and beta adrenergic receptors during resuscitation. *Crit Care Med* 1979;7(7):293-6.
- Michael JR, Guerci AD, Koehler RC, Shi AY, Tsitlik J, Chandra N, et al. Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. *Circulation* 1984;69(4):822-35.
- Ditchey RV, Lindenfeld J. Failure of epinephrine to improve the balance between myocardial oxygen supply and demand during closed-chest resuscitation in dogs. *Circulation* 1988;78(2):382-9.
- Beck C, Leightner D. Reversal of death in good hearts. *J Cardiovasc Surg* 1962;3:27-30.
- Beck CS, Rand HJ 3<sup>rd</sup>. Cardiac arrest during anesthesia and surgery. *J Am Med Assoc* 1949;141(17):1230-3.
- Gerbode F. The cardiac emergency. *Ann Surg* 1952;135:431.
- Lindner KH, Ahnefeld FW, Bowdler IM. Comparison of different doses of epinephrine on myocardial perfusion and resuscitation success during cardiopulmonary resuscitation in a pig model. *Am J Emerg Med* 1991;9(1):27-31.
- Brown CG, Werman HA, Davis EA, Hamlin R, Hobson J, Ashton JA. Comparative effect of graded doses of epinephrine on regional brain blood flow during CPR in a swine model. *Ann Emerg Med* 1986;15(10):1138-44.
- Otto CW, Yakaitis RW, Blitt CD. Mechanism of action of epinephrine in resuscitation from asphyxial arrest. *Crit Care Med* 1981;9(4):321-4.
- Stiell IG, Hebert PC, Weitzman BN, Wells GA, Raman S, Stark RM, et al. High-dose epinephrine in adult cardiac arrest. *N Engl J Med* 1992;327(15):1045-50.
- Callahan M, Madsen CD, Barton CW, Saunders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. *JAMA* 1992;268(19):2667-72.
- Lindner KH, Ahnefeld FW, Prengel AW. Comparison of standard and high-dose adrenaline in the resuscitation of asystole and electromechanical dissociation. *Acta Anaesthesiol Scand* 1991;35(3):253-6.
- Hoekstra JW, Griffith R, Kelley R, Cody RJ, Lewis D, Scheatzle M, et al. Effect of standard-dose versus high-dose epinephrine on myocardial high-energy phosphates during ventricular fibrillation and closed-chest CPR. *Ann Emerg Med* 1993;22(9):1385-91.
- Choux C, Gueugniaud PY, Barbieux A, Pham E, Lae C, Dubien PY, et al. Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital. *Resuscitation* 1995;29(1):3-9.
- Sherman BW, Munger MA, Foulke GE, Rutherford WF, Panacek EA. High-dose versus standard-dose epinephrine treatment of cardiac arrest after failure of standard therapy. *Pharmacotherapy* 1997;17(2):242-7.
- Gueugniaud PY, Mols P, Goldstein P, Pham E, Dubien PY, Deweerdt C, et al. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. *European Epinephrine Study Group. N Engl J Med* 1998;339(22):1595-601.
- Rivers EP, Wortsman J, Rady MY, Blake HC, McGeorge FT, Buderer NM. The effect of the total cumulative epinephrine dose administered during human CPR on hemodynamic, oxygen transport, and utilization variables in the postresuscitation period. *Chest* 1994;106(5):1499-507.
- Behringer W, Kittler H, Sterz F, Domanovits H, Schoerhuber W, Holzer M, et al. Cumulative epinephrine dose during cardiopulmonary resuscitation and neurologic outcome. *Ann Intern Med* 1998;129(6):450-6.
- Hörnchen U, Lussi C, Schüttler J. Potential risks of high-dose epinephrine for resuscitation from ventricular fibrillation in a porcine model. *J Cardiothorac Vasc Anesth* 1993;7(2):184-7.
- Neumar RW, Bircher NG, Sim KM, Xiao F, Zadach KS, Radovsky A, et al. Epinephrine and sodium bicarbonate during CPR following asphyxial cardiac arrest in rats. *Resuscitation* 1995;29(3):249-63.
- Schmitz B, Fischer M, Bockhorst K, Hoehn-Berlage M, Hossmann KA.

- Resuscitation from cardiac arrest in cats: influence of epinephrine dosage on brain recovery. *Resuscitation* 1995;30(3):251-62.
24. Roberts JR, Greenberg MI, Knaub MA, Kendrick ZV, Baskin SI. Blood levels following intravenous and endotracheal epinephrine administration. *JACEP* 1979;8(2):53-6.
  25. Aitkenhead AR. Drug administration during CPR: What route? *Resuscitation* 1991;22:191-5.
  26. Paradis NA, Martin GB, Rivers EP, Goetting MG, Appleton TJ, Feingold M, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA* 1990;263(8):1106-13.
  27. Cummins RO, LoGerfo JP, Inui TS, Weiss NS. High-yield referral criteria for posttraumatic skull roentgenography. Response of physicians and accuracy of criteria. *JAMA* 1980;244(7):673-6.
  28. Parmley WW, Chatterjee K, Charuzi Y, Swan HJ. Hemodynamic effects of noninvasive systolic unloading (nitroprusside) and diastolic augmentation (external counterpulsation) in patients with acute myocardial infarction. *Am J Cardiol* 1974;33(7):819-25.
  29. Durrer JD, Lie KI, van Capelle FJ, Durrer D. Effect of sodium nitroprusside on mortality in acute myocardial infarction. *N Engl J Med* 1982;306(19):1121-8.
  30. Cohn JN, Franciosa JA, Francis GS, Archibald D, Tristani F, Fletcher R, et al. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: Results of a Veterans Administration cooperative study. *N Engl J Med* 1982;306(19):1129-35.
  31. Lie KI, Durrer JD, van Capelle FJ, Durrer D. Nitroprusside and heart failure complicating acute myocardial infarction. *Eur Heart J* 1983;4Suppl A:209-10.
  32. Chiariello M, Gold HK, Leinbach RC, Davis MA, Maroko PR. Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction. *Circulation* 1976;54(5):766-73.
  33. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. *JAMA* 1988;260(14):2088-93.
  34. Lindner KH, Strohmenger HU, Ensinger H, Hetzel WD, Ahnefeld FW, Georgieff M. Stress hormone response during and after cardiopulmonary resuscitation. *Anesthesiology* 1992;77(4):662-8.
  35. Lindner KH, Haak T, Keller A, Bothner U, Lurie KG. Release of endogenous vasopressors during and after cardiopulmonary resuscitation. *Heart* 1996;75(2):145-50.
  36. Babar SI, Berg RA, Hilwig RW, Kern KB, Ewy GA. Vasopressin versus epinephrine during cardiopulmonary resuscitation: A randomized swine outcome study. *Resuscitation* 1999;41(2):185-92.
  37. Strohmenger HU, Lindner KH, Prengel AW, Pfenninger EG, Bothner U, Lurie KG. Effects of epinephrine and vasopressin on median fibrillation frequency and defibrillation success in a porcine model of cardiopulmonary resuscitation. *Resuscitation* 1996;31(1):65-73.
  38. Prengel AW, Lindner KH, Keller A, Lurie KG. Cardiovascular function during the postresuscitation phase after cardiac arrest in pigs: A comparison of epinephrine versus vasopressin. *Crit Care Med* 1996;24(12):2014-9.
  39. Wenzel V, Lindner KH, Prengel AW, Maier C, Voelckel W, Lurie KG, et al. Vasopressin improves vital organ blood flow after prolonged cardiac arrest with postcountershock pulseless electrical activity in pigs. *Crit Care Med* 1999;27(3):486-92.
  40. Fox AW, May RE, Mitch WE. Comparison of peptide and nonpeptide receptor-mediated responses in rat tail artery. *J Cardiovasc Pharmacol* 1992;20(2):282-9.
  41. Oyama H, Suzuki Y, Satoh S, Kajita Y, Takayasu M, Shibuya M, et al. Role of nitric oxide in the cerebral vasodilatory responses to vasopressin and oxytocin in dogs. *J Cereb Blood Flow Metab* 1993;13(2):285-90.
  42. Wenzel V, Linder KH, Augenstein S, Prengel AW, Strohmenger HU. Vasopressin combined with epinephrine decreases cerebral perfusion compared with vasopressin alone during cardiopulmonary resuscitation in pigs. *Stroke* 1998;29(7):1462-7; discussion 1467.
  43. Wenzel V, Lindner KH, Baubin MA, Voelckel WG. Vasopressin decreases endogenous catecholamine plasma concentrations during cardiopulmonary resuscitation in pigs. *Crit Care Med* 2000;28(4):1096-100.
  44. Morris DC, Dereczyk BE, Grzybowski M, Martin GB, Rivers EP, Wortsman J, et al. Vasopressin can increase coronary perfusion pressure during human cardiopulmonary resuscitation. *Acad Emerg Med* 1997;4(9):878-83.
  45. Lindner KH, Prengel AW, Pfenninger EG, Lindner IM, Strohmenger HU, Georgieff M, et al. Vasopressin improves vital organ blood flow during closed-chest cardiopulmonary resuscitation in pigs. *Circulation* 1995;91(1):215-21.
  46. Wenzel V, Lindner KH, Prengel AW, Lurie KG, Strohmenger HU. Endobronchial vasopressin improves survival during cardiopulmonary resuscitation in pigs. *Anesthesiology* 1997;86(6):1375-81.
  47. Wenzel V, Lindner KH, Augenstein S. Intraosseous vasopressin improves coronary perfusion pressure rapidly during cardiopulmonary resuscitation in pigs. *Crit Care Med* 1999;27:1565-9.
  48. Voelckel WG, Lindner KH, Wenzel V, Bonatti JO, Krismer AC, Miller EA, et al. Effect of small-dose dopamine on mesenteric blood flow and renal function in a pig model of cardiopulmonary resuscitation with vasopressin. *Anesth Analg* 1999;89(6):1430-6.
  49. Lindner KH, Prengel AW, Brinkmann A, Strohmenger HU, Lindner IM, Lurie KG. Vasopressin administration in refractory cardiac arrest. *Ann Intern Med* 1996;124(12):1061-4.
  50. Argenziano M, Chen JM, Cullinane S, Choudhri AF, Rose EA, Smith CR, et al. Arginine vasopressin in the management of vasodilatory hypotension after cardiac transplantation. *J Heart Lung Transplant* 1999;18(8):814-7.
  51. Morales DL, Gregg D, Helman DN, Williams MR, Naka Y, Landry DW, et al. Arginine vasopressin in the treatment of 50 patients with postcardiotomy vasodilatory shock. *Ann Thorac Surg* 2000;69(1):102-6.